APPENDIX A: CLAIMS IN APPLICATION NO.: 09/743,492

1. A monoclonal antibody having specificity to both an intracellular domain of LAR and an intracellular domain of CD45.

2-4. (canceled)

5. The antibody according to claim 1 having specificity to phosphatase domains of protein tyrosine phosphatases.

6. The antibody according to claim 1, which is generated using a polypeptide that is encoded by a nucleotide sequence set forth in SEQ ID NO: 1.

7. (canceled)

8. (canceled)

9. The antibody according to claim 1 wherein the antibody is generated using a GST-LAR phosphatase domain fusion protein as an immunogen.

10. The antibody according to claim 9 wherein the GST-LAR phosphatase domain fusion protein is produced by: culturing *Escherichia coli* transformed or transfected with an expression vector comprising a coding region of GST gene and a coding region of a phosphatase domain of LAR gene at 20-30°C for 16-24 hours; and isolating the fusion protein from the culture fluid and/or bacterial cells.

11. The antibody according to claim 10 wherein the GST-LAR phosphatase domain fusion protein is further purified based on an affinity to a support carrying glutathione, and the elution of said fusion protein from the support is performed by boiling in the presence of a detergent.

12. The antibody according to claim 9 wherein screening of the antibody that was generated using the GST-LAR phosphatase domain fusion protein as an immunogen is performed using said fusion protein.

13. A monoclonal antibody having specificity to an intracellular domain of a protein tyrosine phosphatase, which is produced by a hybridoma with Accession No. FERM BP-6344.

14. The antibody according to claim 1 having a molecular weight of about 146 kDA.

15. A hybridoma cell line that produces the monoclonal antibody according to claim 1.

16. A hybridoma cell line with Accession No. FERM BP-6344.

17. (canceled)

18. A method for generating an antibody according to claim 1, comprising the step of:

immunizing an animal with a GST-LAR phosphatase domain fusion protein;

preparing a hybridoma cell line from an antibody-producing cell obtained from the immunized animal; and

producing a monoclonal antibody from the hybridoma cell line.

19. The method according to claim 18 wherein the GST-LAR phosphatase domain fusion protein is produced by: culturing *Escherichia coli* transformed or transfected with an expression vector comprising a coding region of GST gene and a coding region of a phosphatase domain of LAR gene at 20-30°C for 16-24 hours; and isolating the fusion protein from the culture fluid and/or bacterial cells.

20. The method according to claim 19 wherein the GST-LAR phosphatase domain fusion protein is further purified based on an affinity to a support carrying glutathione, and the elution of said fusion protein from the support is performed by boiling in the presence of a detergent.

21. The method according to claim 18, further comprising the step of:

screening antibodies generated in the producing step using said GST-LAR phosphatase domain fusion protein.

22-30. (canceled)

6 **Utilization of antibodies for DDS (Drug Delivery System)**

Id als of all pharmaceuticals involve their actions which are directed just to the target tissue or target cells, with no action at all on other tissues or cells in either positive or negative fashion. This shall be necessary requirement for such types of agents as anticancer agents which kill the target cells, in particular. In addition to the anticancer agents, upon therapies in which particular cell clone in the immune system, which is a cause of autoimmune diseases should be eliminated, use of the agents is limited in light of their side effects unless they have high target directional characteristics.

Antibodies are originally substances that are responsible for the defense mechanisms in vivo, which are present in a living body. They form an antibody-antigen complex via binding to an antigen, and thus lyse/disrupt the antigen in cooperation with complements or cells such as macrophage. Even though an antibody is used alone, suppression of cancer cells has been also observed in some instances in which suitable antibodies are used [for example, progression of leukemia was inhibited by a made-to-order monoclonal antibody (anti-idiotypic antibody) against B lymphocytic leukemia[1]]. However, the administration of a monoclonal antibody alone generally results in weak suppressive effects against cancer cells.

A vari ty of grounds therefor can be envisaged:

(1) Monoclonal antibody does not reach to cancer cells at a sufficient concentration.

(2) Because metabolism of the monoclonal antibody by a host is rapidly caused, a large amount of the antibody must be successively administered.

(3) Expression amount of the target antigen to be expressed on the cancer cell surface is originally low. Alternatively, the target antigen is decreased in terms of its expression amount, or qualitatively altered, in connection with the therapy.

(4) Cooperative action in the host such as those of complements or macrophage is weak when the antibody used is derived from a mouse.

(5) Production of an anti-mouse immunoglobulin antibody may lead to disablement of the used antibody or also may result in a side effect.

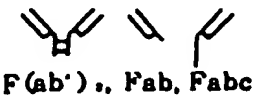
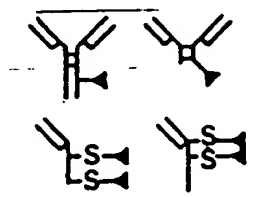
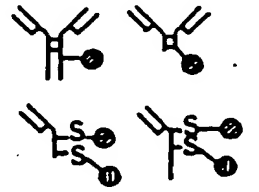
In these respects, development of target directed agents has been actively conducted, which comprise a monoclonal antibody-active drug complex in which a monoclonal antibody is merely used for the leading action to the target cells, whilst other drug is utilized for disrupting the target cells in order to improve the effects.

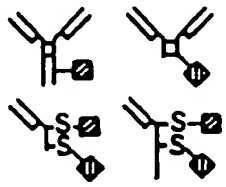
Ideas for agents having target directivity such as leading missiles (magic bullet) were envisaged since the initial time when the presence of antibodies was revealed. Mode of using antibodies upon utilization of the antibody as an antigen-specific cytocidal agent may include such modes as shown in Table 6.1.

[Table 6.1] Method of utilizing monoclonal antibodies

--Illustrative Conception on Embodiment to be utilized as antigen-specific cytocidal agent--

No.	Utilization Mode	Conceptual diagram	Notes
1	Unlabeled antibody	 Complete molecule of immunoglobulin (in addition to the antigen binding capacity of Fab fragment, biological activity of Fc fragment is also expected in 2) and 3)).	1) Disappearance of biological activity of the antigen through binding to the target antigen. 2) Disruption of the target by cooperating action of a complement system in vivo. 3) ADCC action by Fc receptor-carrying cell disabling cells in vivo.

2	Molecule fragment of unlabeled antibody		1) Disappearance of biological activity of the antigen through binding to the target antigen (with low expectation to the effects).
3	Agent-bound and target directed (naked type agent)		1) Missile type agent by way of combining the antigen binding specificity of the antibody and disruptive ability on target cells of the agent.
4	Fine particle containing agent-bound and target directed (coating type agent)		1) Binding of the agent and the antibody molecule through conjugating the agent with ribosome or synthetic macromolecule fine particles. In addition to the increase in the amount of transported agent per 1 molecule of the antibody, to avoid accidental disruption of cells other than the targeted cell during the transport is also expected.

5	Target directed aiming at local activation of prodrug (local activation type agent)		1) As a substance bound to the antibody, a prodrug of indiscriminately disruptive agent is separately used, which does not directly act on disruption of the target, and the antibody is bound to a substance which functions to activate the prodrug at an antibody accumulation site.